REMARKS

Claims 1, 4-10, 12-17, 21, 23-38, and 41-49 were pending in this application. Claims 1, 6, 43, 44, and 49 have been amended. Please cancel claims 5, 13-16, 21, 23-27, 31-38, 47, and 48. New claims 50-68 have been added. Therefore, claims 1, 4, 6-10, 12, 17, 29, 30, 39, 41-46, and 49-68 will be pending upon entry of the instant amendment.

Claims 13-16, 21, 23-27, 31-38, and 48 have been cancelled for being directed to a non-elected invention. Support for the amendments to

The specification has been amended to correct for typographical errors identified by the Examiner. The description of Figure 2 has been amended to reference the symbol shown at the end of the amino acid sequences described in the figure. The abstract of the specification has been amended to delete use of the word "said" and other improper language used in the abstract.

Figures 2, 19a, 19b, and 25-27 have also been amended in compliance with 37 CFR 1.121(d). Figures 2 and 25-27 have been amended to exclude shading per the Examiner's request (shading is shown in Annotated Sheets enclosed herewith). Annotated versions of Figures 19a and 19b have not been provided, as the Replacement Sheets enclosed herewith provide clearer versions than those previously submitted. No new matter has been added, and entry of the replacement drawings and amended specification is respectfully requested.

No new matter has been added. Entry of the replacement drawings, amended specification, and claim amendments is respectfully requested. Cancellation of and/or amendments to the claims should in no way be construed as an acquiescence to any of the Examiner's objections and/or rejections. The cancellation of and/or amendments to the claims are being made solely to expedite prosecution of the above-identified application. Applicants reserve the option to further prosecute the same or similar claims in the present or another patent application. Applicant further maintains the right to file the canceled claims directed to non-elected invention, *i.e.*, claims 13-16, 21, 23-27, 31-38, and 48, in future divisional applications. The amendments made to the claims are not related to any issues of patentability.

Rejection of Claims 1, 4-10, 12, 17, 28-30, 41-47, and 49 Under 35 USC 112, First Paragraph

The Examiner has rejected claims 1, 4-10, 12, 17, 28-30, 41-47, and 49 under 35 U.S.C. § 112, first paragraph for lack of enablement. The Examiner acknowledges that the specification enables "a recombinant fusion peptabody which binds to an epidermal growth factor receptor comprising a specific portion of a cartilage oligomer matrix protein (49 amino acids...), a specific portion of a hinge region of an immunoglobulin polypeptide (19 amino acids from human IgA...), an enhancer sequence, and an epidermal growth factor receptor ligand." The Examiner suggests, however, that the specification fails to provide enablement for a peptabody comprising "any portion of a cartilage matrix protein" or "just any portion of a hinge regions of an immunoglobulin polypeptide." Applicant respectfully traverses this rejection.

First, Applicant notes that claim 43 (and new claims 50-58 which depend therefrom) has been amended to specify a recombinant fusion peptabody, which binds to the epidermal growth factor receptor ErbB-1 comprising a human cartilage oligomer matrix polypeptide (COMP) *comprising amino acid residues 16 to 64 of SEQ ID NO: 1*; a peptide enhancer sequence for increasing protein production, located at the N terminus of the peptabody and having a sequence selected from the group consisting of YSFE, YSFEDL, YSFEDLY, YSFEDLYR, and YSFEDLYRR; a portion of a hinge region of an immunoglobulin polypeptide *comprising amino acid residues 65 to 83 of SEQ ID NO: 1,* located at the C terminus of the portion of the cartilage oligomer matrix polypeptide; and an epidermal growth factor receptor ligand located at the C terminus of the hinge region, wherein said recombinant fusion peptabody is capable of inducing cellular death in a cell expressing the epidermal growth factor receptor. New claim 59 (and new claims 60-68 that depend therefrom) is directed to a peptabody specific to ErbB-3 or ErbB-4, and also requires specific sequences in COMP and the Ig hinge region of the peptabody.

Claim 1 (and claims 4, 6-10, 12, 17, 28-30, and new claim 69) has been amended to specify a recombinant fusion peptabody, which binds to an epidermal growth factor receptor selected from the group consisting of ErbB-1, ErbB-3, and or ErbB-4, *comprising a portion of a cartilage oligomer matrix polypeptide which is capable of oligomerizing; a peptide enhancer sequence having an amino acid sequence selected from the group consisting of*

YSFE, YSFEDL, YSFEDLY, YSFEDLYR, and YSFEDLYRR, and located at the N terminus of the peptabody; a portion of a hinge region of an immunoglobulin polypeptide located at the C terminus of the portion of the cartilage oligomer matrix polypeptide; and *an epidermal growth factor receptor ligand which can bind to the epidermal growth factor receptor,* located at the C terminus of the hinge region, wherein said recombinant fusion peptabody is capable of inducing cellular death in a cell expressing said epidermal growth factor receptor.

As amended, claim 44 (and claim 45 and 46 that depend therefrom), is directed to a monomer of a peptabody comprising *a portion of a cartilage oligomer matrix polypeptide which is capable of oligomerizing*; an *enhancer peptide sequence having an amino acid sequence selected from the group consisting of YSFE, YSFEDL, YSFEDLY, YSFEDLYR, and YSFEDLYRR,* and located at the N terminus of the peptabody; a portion of a hinge region of an immunoglobulin polypeptide located at the C terminus of the portion of the cartilage oligomer matrix polypeptide; and an epidermal growth factor receptor ligand located at the C terminus of the hinge region, wherein the epidermal growth factor receptor ligand binds to an epidermal growth factor receptor selected from the group consisting of ErbB-1, ErbB-3 or ErbB-4.

Amended claim 49 is directed to an isolated and recombinant fusion peptabody, which binds to an epidermal growth factor receptor selected from the group consisting of ErbB-1, ErbB-3, and ErbB-4, comprising a portion of a *humanized or human cartilage oligomer matrix polypeptide which is capable of oligomerizing*; *a peptide enhancer sequence having an amino acid sequence selected from the group consisting of YSFE, YSFEDL, YSFEDLY, YSFEDLYR, and YSFEDLYRR* and located at the N terminus of the portion of the cartilage oligomer matrix polypeptide; a *portion of a hinge region comprising 19 amino acids of an immunoglobulin polypeptide,* located at the C terminus of the portion of the cartilage oligomer matrix polypeptide; and an epidermal growth factor receptor ligand located at the C terminus of the hinge region, wherein said isolated and recombinant fusion peptabody is capable of inducing cellular death in a cell expressing said epidermal growth factor receptor.

Thus, each of independent claims 1, 44, and 49, as well as new claim 59, requires that the peptabody of the invention include an enhancer sequence having an amino acid sequence selected from the group consisting of YSFE, YSFEDL, YSFEDLY, YSFEDLYR, and

YSFEDLYRR, a portion of the COMP which is capable of oligomerizing, and a EGF receptor ligand which is capable of binding the EGF receptor.

With respect to the Examiner's assertion that the specification fails to provide "any direction or guidance to assist one skilled in the art in the selection of all possible portions of the oligomeric matrix polypeptide or the hinge region," Applicant respectfully disagrees.

While Applicant asserts that the claims as originally written were fully enabled under the requirements set forth in 35 USC 112, first paragraph, the claims have been amended to require that the portion of the COMP have a specific functional characteristic, *i.e.,* that the COMP portion can oligomerize. As described at page 19, lines 16-32, the COMP region of the peptabody imparts the ability of the protein to oligomerize. Applicant provides working examples of peptabodies that contain such COMP sequences. In view of the amendment to the claims, Applicant respectfully submits that the claims are fully enabled with respect to the COMP portion of the peptabody.

With respect to the hinge portion of the claimed peptabody, Applicant submits that one of ordinary skill in the art would be able to make and use the claimed invention without undue experimentation. The specification teaches that the hinge is used as a spacer between protein domains. The specification provides an example of such a spacer, *i.e.,* a 19 amino acid hinge derived from an Ig. Applicant notes that claim 49 has been amended to specify that the hinge region comprise 19 amino acids of an immunoglobulin polypeptide.

Regarding the questions posed by the Examiner at page 7 of the Office Action, Applicant provides the following. The first question asked whether the peptabody comprising any of the ligands would bind to an EGF-R. Applicant notes that claims 1, 6, 43, 44, 49 and new claims 51 and 59, each require that the EGF receptor ligand portion of the peptabody be able to bind the EGF receptor. At page 18, lines 23-31, the specification describes characteristics of functional forms of EGF ligands.

The second question posed by the Examiner asked whether the length of the polypeptide portions would affect the folding or function of the claimed peptabody. As stated above, Applicant describes the hinge as a spacer between the domains, and also provides a working example of such a linker, *i.e.,* a 19 amino acid hinge derived from an Ig. One of ordinary skill in the art would recognize that such a linker could be replaced in sequence and/or length without undue experimentation. Furthermore, the specification

teaches that it is the *position* of the linker that is significant in achieving the invention (see page 20, lines 7-14).

With respect to the art cited by the Examiner as teaching unpredictability in view of Applicant's invention, Applicant submits that three of the references (Burgess *et al.*, Schwartz *et al.*, and Lazar *et al.*) address topics which are not presented by the instant invention, *i.e.*, effects of mutations on protein structure. With respect to the Lin *et al.* reference cited for establishing unpredictability for teaching that a protein may lose its binding ability upon removal of a single amino acid, Applicant notes that the claims have been amended to require that the EGF receptor ligand, or portion thereof, retain the ability to bind the receptor. With respect to Fattah *et al.* cited by the Examiner, Applicant notes that the claims have been amended to require specific enhancer sequences identified by Applicant as having advantageous characteristics.

Applicant notes that claim 41 is specific to the enhancer sequences identified in the instant specification. Appropriate clarification with respect to the enablement rejection in view of this claim is respectfully requested.

Based on the teachings in the specification and the knowledge in the art at the time of filing, Applicant submits that one of ordinary skill in the art would not have to perform undue experimentation to arrive at the invention described in claims 1, 4-10, 12, 17, 28-30, 41-47, and 49. Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claims 1, 4-10, 12, 17, 28-30, 41-47, and 49 for lack of enablement.

Rejection of Claims 1, 4, 6-10, 17, 44-46, and 49 Under 35 USC 103(a)

The Examiner has rejected claims 1, 4, 6-10, 17, 44-46, and 49 under 35 USC § 103(a) as being unpatentable over Houimel *et al.* (*Int J Cancer* (2001) 92:748) in view of Azevedo *et al.* (*Brazilian J of Medical and Biological* Research (1999) 32:147). The Examiner suggests that Houimel describes "a recombinant peptabody comprising peptide sequences that bind Erb-2, the coiled-coil assembly domain of the human cartilage oligomeric matrix protein (hCOMP), a hinge region derived from human IgA1, and a his6-tag." Azevedo is cited to make up for the deficiencies of Houimel, specifically the lack of teachings of an enhancer sequence. Applicant respectfully traverses the rejection.

Independent claims 1, 44, 46, and 49 (and claims that depend therefrom) have been amended to specify that the peptide enhancer recited in each claim *have an amino acid sequence selected from the group consisting of YSFE, YSFEDL, YSFEDLY, YSFEDLYR, and YSFEDLYRR* and located at the N terminus of the peptabody.

A proper *prima facie* obviousness rejection requires that there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Additionally, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. See M.P.E.P. § 2143. Also, see In re Vaeck, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1443 (Fed. Cir. 1991) (the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in Applicant's disclosure).

Applicant respectfully submits that the proposed references, either alone or in combination, fail to provide a specific teaching or suggestion of the unique structural features of Applicant's claimed proteins. None of these cited references teach or suggest a peptabody comprising a peptide enhancer recited in each claim have an amino acid sequence selected from the group consisting of YSFE, YSFEDL, YSFEDLY, YSFEDLYR, and YSFEDLYRR, as required by the amended claims. Thus, the combination of cited references fail to satisfy all of the elements required under 35 USC §103.

In view of the above, Applicant submits that none of the cited references, either alone or in combination, teach or suggest the claimed peptabody molecules. Thus, Applicant respectfully requests that the rejection of claims 1, 4, 6-10, 17, 44-46, and 49 under 35 USC 103(a) be reconsidered and withdrawn.

Rejection of Claims 1, 4, 6-10, 17, 28-30, 44-46, and 49 Under 35 USC 103(a)

The Examiner has rejected claims 1, 4, 6-10, 17, 28-30, 44-46, and 49 under 35 USC § 103(a) as being unpatentable over Houimel *et al.* (*Int J Cancer* (2001) 92:748) in view of Azevedo *et al.* (*Brazilian J of Medical and Biological* Research (1999) 32:147) and in further view of Goins *et al.* (US Patent Publication No. 2002/0164648). The Examiner suggests that Houimel describes "a recombinant peptabody comprising peptide sequences that bind Erb-2,

the coiled-coil assembly domain of the human cartilage oligomeric matrix protein (hCOMP), a hinge region derived from human IgA1, and a his6-tag." Azevedo is cited to make up for the deficiencies of Houimel, specifically the lack of teachings of an enhancer sequence. Goins is cited to make up for the deficiencies of both Houimel and Azevedo with respect to pharmaceutical compositions and kits. Applicant respectfully traverses the rejection.

As described above, independent claims 1, 44, 46, and 49 (and claims that depend therefrom) have been amended to specify that the peptide enhancer recited in each claim *have an amino acid sequence selected from the group consisting of YSFE, YSFEDL, YSFEDLY, YSFEDLYR, and YSFEDLYRR* and located at the N terminus of the peptabody.

Applicant respectfully submits that the proposed references, either alone or in combination, fail to provide a specific teaching or suggestion of the unique structural features of Applicant's claimed proteins. None of these cited references teach or suggest a peptabody comprising a peptide enhancer recited in each claim have an amino acid sequence selected from the group consisting of YSFE, YSFEDL, YSFEDLY, YSFEDLYR, and YSFEDLYRR, as required by the amended claims. Thus, the combination of cited references fail to satisfy all of the elements required under 35 USC §103.

In view of the above, Applicant submits that none of the cited references, either alone or in combination, teach or suggest the claimed peptabody molecules. Thus, Applicant respectfully requests that the rejection of claims 1, 4, 6-10, 17, 28-30, 44-46, and 49 under 35 USC 103(a) be reconsidered and withdrawn.

SUMMARY

It is respectfully submitted that this application is in condition for allowance. If there are any remaining issues, or if the Examiner believes that a telephone conversation with Applicant's attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned at (617) 227-7400. Please charge any additional fees or credit any overpayments to our Deposit Account No. 12-0080, under Order No. KZI-002US from which the undersigned is authorized to draw.

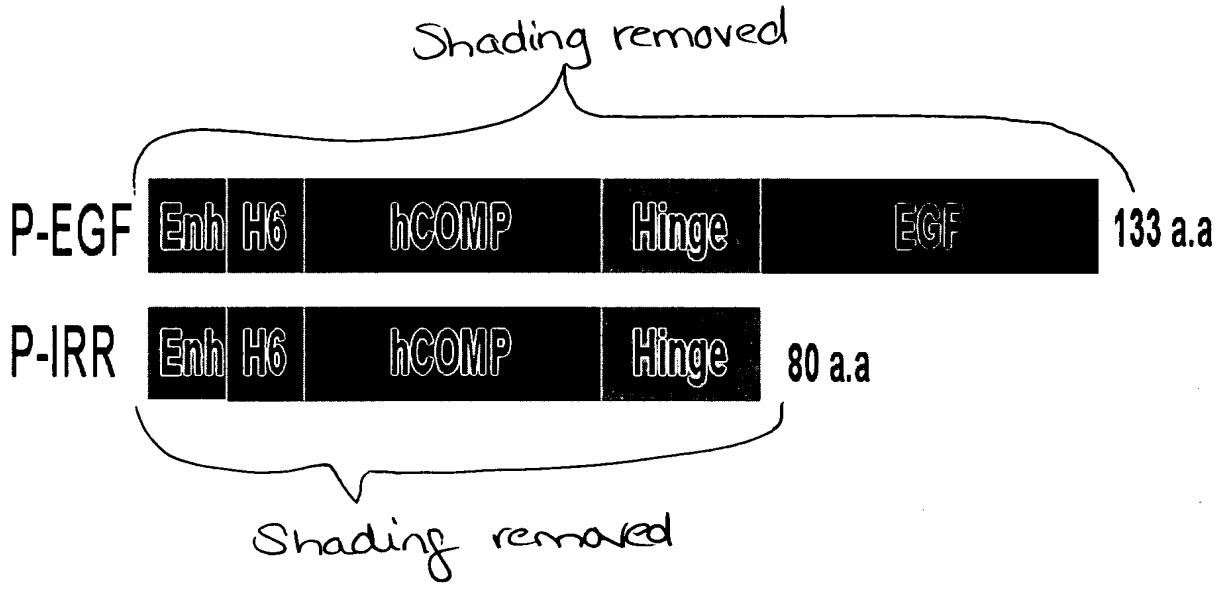
Dated: November 16, 2007

Respectfully submitted,

By _____

Cristin E. Howley, Ph.D.
Registration No.: 55,281
LAHIVE & COCKFIELD, LLP
One Post Office Square
Boston, Massachusetts 02109-2127
(617) 227-7400
(617) 742-4214 (Fax)
Agent For Applicants

Figure 2:



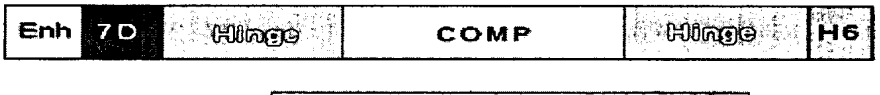
Amino acid sequence of peptabody Irrelevant :
MYSFEDLHHHHHHGDLGPQMLRELQETNAALQDVRDYLRQLVREIT
FLKNTVMECDACGMQQTSPPTPPTPSPSTPPTPSPRS*

Amino acid sequence of peptabody EGF :
MYSFEDLHHHHHHGDLGPQMLRELQETNAALQDVRDYLRQLVREIT
FLKNTVMECDACGMQQTSPPTPPTPSPSTPPTPSPRSNSDSECPLSH
DGHCLHDGVCMYIEALDKYACNCVVGYIGERCQYRDLKWWELR*

Annotated Sheet

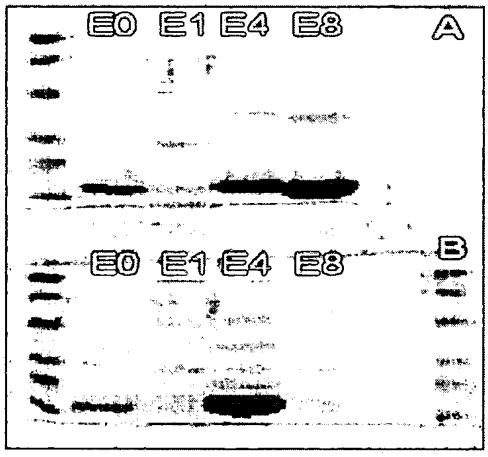
Figure 25:

Production of decabodies fused to different Enhancers



Enh0 = -
Enh1 = YSF
Enh4 = YSFEDL
Enh8 = YSFEDLYRR

7D = peptide STNHNR

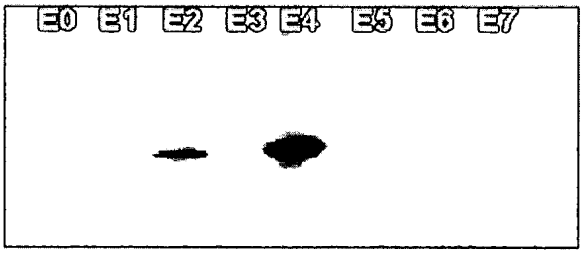


Shading removed

Figure 26:

Production of peptabodies fused to different Enhancers

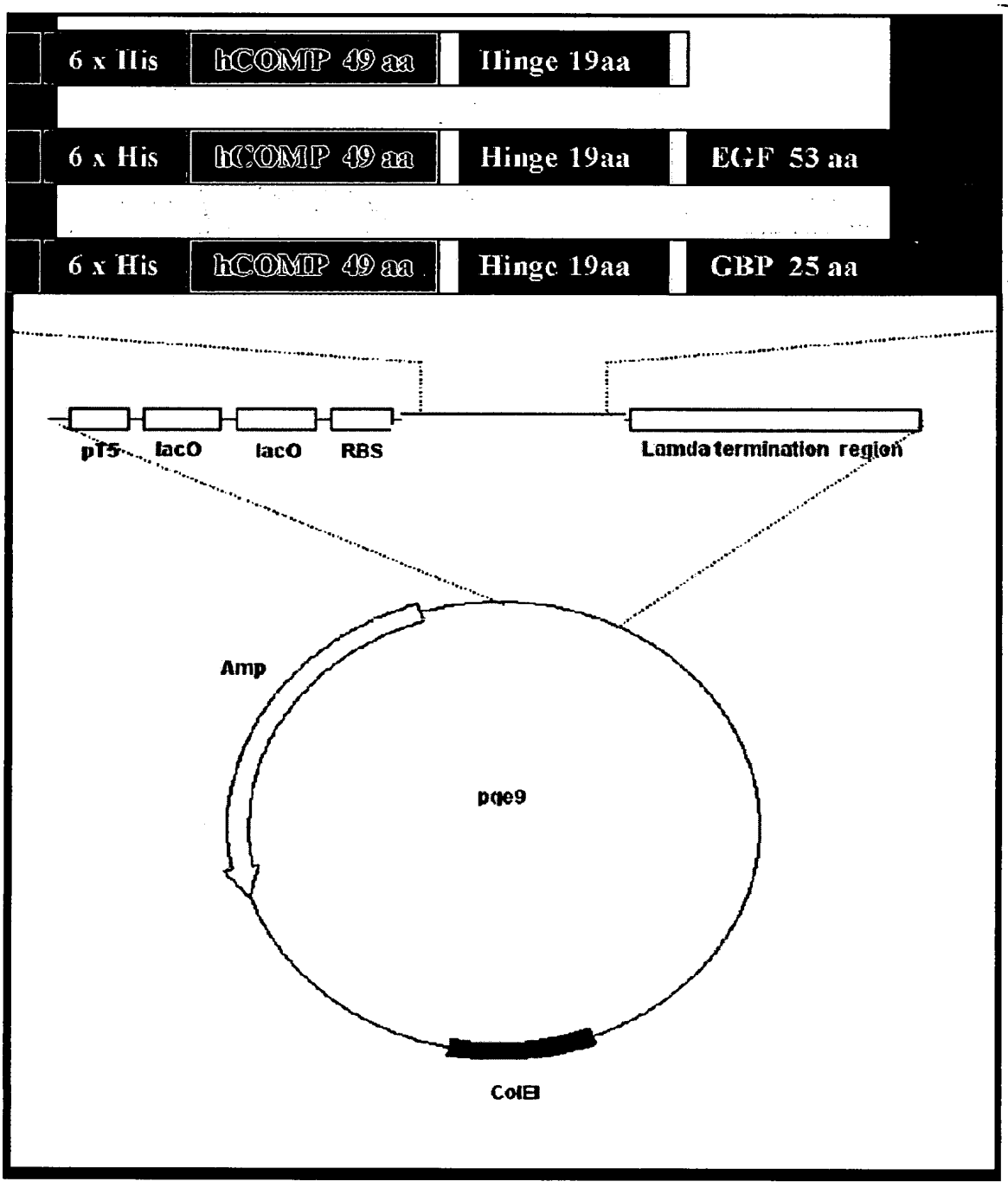
Enh0 = -
Enh1 = Y S F
Enh2 = Y S F E
Enh3 = Y S F E D
Enh4 = Y S F E D L
Enh5 = S F E D L
Enh6 = F E D L
Enh7 = E D L



Shading removed

Annotated Sheet

Figure 27:


6 x His
hCOMP 49 aa
Hinge 19aa
6 x His
hCOMP 49 aa
Hinge 19aa
EGF 53 aa
6 x His
hCOMP 49 aa
Hinge 19aa
GBP 25 aa
Shading removed
pT5
lacO
lacO
RBS
Lamda termination region
Amp
pqe9
ColEI